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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	PROTECTIVE LAYERS COMPATIBLE WITH THICK FILM PASTES

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or
☑ Application No. 10/713606, filed on November 14, 2003,

☐ as amended on _____(if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/ we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: YOUNG H. KIM

Signature: Yg H Kim Citizen of: ~~KR~~ USA

Inventor two: _____

Signature: _____ Citizen of: _____

Inventor three: _____

Signature: _____ Citizen of: _____

Inventor four: _____

Signature: _____ Citizen of: _____

☐ Additional inventors are being named on _____additional form(s) attached hereto.

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Application Number	10/713606
Filing Date	November 14, 2003
First Named Inventor	Young H. Kim
Title	PROTECTIVE LAYERS COMPATIBLE WITH THICK FILM PASTES
Art Unit	1752
Examiner Name	
Attorney Docket Number	CL2229USNA

I hereby appoint:

☑ Practitioners at Customer Number: **23906**

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

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I am the:

☐ Applicant/Inventor.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Name	Young H. Kim		
Signature	Young H. Kim		
Date	3/17/2004	Telephone	302-695-3263

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

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STARCH-BASED DRUG DELIVERY SYSTEMS

Remon, J.P.; Voorspels, J.; Radeloff, M.; Patel, A.N.; Beck, R.

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TEXT:

Starch is a heterogeneous material consisting of two types of polymers; amylose and amylopectin. Amylose is essentially linear and amylopectin has a branched structure. The ratio of amylose to amylopectin found in starches varies depending upon the source. Most starches such as maize, wheat and potato contain 18-28% amylose. Certain starches - for instance, special hybrids of maize such as waxy maize - are essentially composed of amylopectin. State-of-the-art starch processing allows correction of these natural variances and guarantees the customer consistent quality in starch raw materials.

STARCH IN CONVENTIONAL DOSAGE FORMS

Starch is one of the most widely used excipients in the manufacture of solid dosage forms and can be used as a filler, a disintegrant or as a binder. Several types of modified starch have been used as tablet excipients, including a physically modified partially hydrolysed starch, starches with a different amy-lose:amylopectin ratio, and oxidised starches.

Starch is still the most commonly used disintegrating agent today. But because of the relatively large amounts of starch required and its lack of compressibility, modified starches were developed and became popular. One example is sodium starch glycolate, a low-substituted derivative of potato starch. Starch has also always been one of the most commonly used granulating agents and is usually used in the form of a paste. The use of cold-water-soluble (also sometimes referred to as drum-dried, roll-dried, cold-water-swellable or pre-gelatinised) waxy maize starch improves binding properties. The ease of dispersion of hydroxypropyl waxy maize starch, for instance, makes it ideal for preparing paste; when added in the dry form no difference in granule quality was observed in comparison with a paste addition.

Research has also been done into the possible use of starch to reduce the quantity of gelatin needed to produce hard gelatin capsules. The material suggested is a dextrin based on waxy maize starch, chemically modified using succinic acid. Another modified starch used for this purpose is hydroxyalkyl starch.

SUSTAINED-RELEASE AGENTS FOR ORAL DRUG DELIVERY

Different types of cold-water-soluble starches were evaluated as a hydrophilic matrix. The effect of the amylose:amylopectin ratio and of the technique and degree of pre-gelatinisation on the final products were studied. Te Wierik, in his work on the application and preparation of linear dextrins, showed that amylodextrin, the metastable amylodextrins and metastable amylose produced tablets with excellent pressure-hardness profiles. He also reported on the successful application of amylodextrin as an excipient in the design of programmed-release tablets.

The release of active substances from both non-porous amylodextrin and metastable amylose tablets is governed by a mechanism of relaxation/controlled penetration of the solvent front in the tablet.

POLYETHYLENE/STARCH EXTRUDATES AS ERODIBLE CARRIERS

Krishnan and co-workers evaluated polyethylene-starch based carriers for sustaining the release of bioactive materials. Polyethylene-starch

carriers were prepared by incorporating various amounts of maize starch in PE beads with and without dye. The granulated mixture was extruded. The dye release could be sustained well over 12 weeks, depending on the percentage starch incorporated. Scanning electron microscopy (SEM) showed gradual erosion of starch particles, leaving a polyethylene skeleton.

Lenaerts and co-workers introduced epichlorohydrin crosslinked amylose as a matrix for controlled release of drugs. A linear release of theophylline from tablets was observed in all cases. A linear increase of the crosslinking degree of the amylose used for tablet preparation generated a non-linear decrease in release time. Analysis of the data indicated that an anomalous release mechanism controlled the drug transport. An hypothesis of a release mechanism controlled by hydrogen association was proposed.

BIOADHESIVE MICROSPHERES

Illum and co-workers reported on bioadhesive microspheres that could not be cleared easily from the nasal cavity. In that system, albumin, starch and DEAE-dextran could be used as the formulation base. Studies have been conducted in human volunteers using a variety of systems containing microspheres with good bioadhesive properties. The microspheres prepared from starch and DEAE-Sephadex were found to be effective in delaying nasal mucociliary clearance. The half-life of clearance for starch microspheres was in the order of 240 min as compared to 15 min for the control formulations. The researchers investigated the possibility of improving the bioavailability of gentamycin administered intranasally by means of starch microspheres. If the gentamycin was administered in combination with the starch microspheres, a significant increase in bioavailability was obtained. An even more dramatic increase was seen when the gentamycin/starch microspheres were administered together with lysophosphatidylcholine.

The bioavailability was increased to about the same as that of the IV dose. Bjork and Edman investigated a nasal delivery system for insulin in rats which used degradable starch microspheres (DSM). Administered nasally as a powder, their preparation gave a dose-dependent reduction in blood glucose and a concomitant increase in serum insulin. Their results indicated that the DSM system offered a means for improving the nasal absorption of drugs. Farraj and coworkers reported that when using starch microsphere bioadhesive systems, the half-time clearance of insulin from the nasal cavity was prolonged to 240 min in comparison to 15 min for a solution. In sheep, the bioavailability of insulin was greatly increased when administered together with microspheres in comparison with an insulin solution.

MAGNETIC STARCH MICROSPHERES

Fahlvik and co-workers reported on the use of magnetic starch microspheres (MSM) for parenteral administration of magnetic iron oxides to enhance contrast in magnetic resonance imaging (MRI), especially by passive targeting of the RES system (spleen and liver). One hour after administration of MSM, all detected radioactivity was seen in the major reticuloendothelial organs. Liver tissues accumulated 84.5% of the doses, whereas 6.5% of the dose was located within the spleen. The biocompatibility of MSM was confirmed. Figure 1 shows the biodistribution of 59Fe labelled MSM and 59Fe labelled degradation products as a percentage of dose per total organ.

STARCH-BASED MICROCAPSULES

Levy and Andy reported on the production of starch microcapsules using a crosslinking process with terephthaloylchloride applied to hydroxyethyl starch (HES) and sodium starch glycolate. It resulted in stable microcapsules whose size could be adjusted by changing the emulsification

parameters. The strength of the wall was shown to depend on polycondensation conditions, mainly pH, terephthaloylchloride concentration and reaction time. HES gave tough membranes, allowing a slow release of encapsulated salicylate. Microcapsules prepared from sodium starch glycolate exhibited hydrophilic properties, as shown by water-induced swelling and gel formation. This property was optimised by introduction of variability in crosslinking parameters. All crosslinked polysaccharide microcapsules were characterised by a total resistance to digestive media. However, the addition of a protein, such as gelatin, to the starch derivatives in the aqueous phase provided biodegradable microcapsules.

BUCCAL BIOADHESIVE TABLET FORMULATION

In order to increase the buccal residence time of miconazole in cases of oral candidiasis, a bioadhesive buccal tablet with slow release properties has been developed. The main advantages of this delivery system are a reduction in the frequency of administration and in the amount of drug administered, which might improve patient compliance. The bioadhesive tablet formulation contained physically modified maize starch (cold-water-soluble waxy maize), Carbopol 934, sodium benzoate and silicon dioxide. The powders were blended and directly compressed. The tablets were 2 mm thick and had a diameter of 7 mm. In several studies miconazole nitrate was used as a model drug for local buccal therapy. Buccal gels containing miconazole nitrate are currently used for the treatment of, for example, oral candidiasis. They must be applied several times a day. The salivary miconazole nitrate concentrations after administration of the bioadhesive tablet and of oral gels were compared (Figs 2a and 2b).

Although the amount of drug administered via the bioadhesive tablet was six times less than when the gel was used, the salivary miconazole levels were higher and remained above the MIC value of Candida albicans for more than 10 hours. The mean adhesive time of the tablet was 586 min. The gum seemed to be the best site for application of the buccal bioadhesive system.

POLYACRYL STARCH MICROPARTICLES AS DRUG CARRIERS

Several papers have dealt with the characterisation, preparation and evaluation of polyacryl starch microparticles as drug carriers. Biodegradable microparticles (mean diameter 0.5 mm) of crosslinked polyacrylate starch (maltodextrin) have been designed as carriers for proteins and low molecular weight drugs in vivo.

It was stated that empty polyacryl starch microparticles were non-immunogenic, but when they were presented to the immune system, together with entrapped human serum albumin, an antibody response was detected: not only against the protein antigen, but also against the microparticle matrix.

Studies in mice have shown that the half-life of the particles in the blood circulation is short (< 5 min) and that they are efficiently taken up by the reticuloendothelial system (mainly in the liver). Particles with many short crosslinks are easily degraded. A high degree of starch derivatisation leads to less degradable particles remaining in the lysosomes of the RES. The possibilities of using polyacryl microparticles as a carrier for low molecular weight drugs have been investigated. Drugs mainly containing primary amino functions (eg primaquine) have been coupled covalently to starch microparticles via tri-, tetra- and pentapeptide spacer arms. The drug-carrier complexes were stable in serum, but free drug was released in the lysosomal fraction. Some problems of bio-compatibility were found, mainly in the liver. It was shown that ester bonds - obtained after derivatisation of starch with acrylic acid chloride are - metabolised in vivo and might form a new basis for a rational design of biodegradable starch microparticles,with crosslinks containing ester bonds.

Using dinitrophenol as a model for a drug, the humoral immunogenicity of the polyacryl starch microparticles was studied in mice - DNP was bound to the particles, directly or via a biodegradable spacer. The study revealed that no major immunological obstacles were seen in using the system, eg in the treatment of parasitic diseases. The antileishmanial effect of microparticle-bound primaquine was demonstrated in mice. The study proved that low molecular weight drugs can be delivered to the liver macrophages, and delivered intralysosomally in an active form, thereby reducing the dose needed to achieve the desired drug effect. Vyas and Jain described the modification of starch microspheres by polymethyl methacrylate grafting. The microspheres contained isosorbide dinitrate (ISDN). The release profile of the drug from the polymer-grafted starch pellets exhibited relatively slow drug release when compared with the release recorded for polyacrylic acid grafted starch. From in vivo evaluation in rabbits, it can be concluded that ISDN could be made available in significantly higher concentrations following buccal administration, and eliminate the peaks and valleys of drug plasma profiles associated with a conventional multiple dosing.

CHEMO-OCCLUSION WITH DEGRADABLE STARCH MICROSPHERES

The use of particulate embolic agents combined with regional chemotherapy in the treatment of hepatocellular carcinoma and metastatic liver cancer has been widely investigated during the past decade. The rationale for the use of such agents is to provide vascular blockade, resulting in a reduced or halted blood flow. This increases the in situ time, tumour exposure and, therefore, the effect of any co-administered cytostatic drug.

Of all the embolic agents and techniques, the degradable starch microspheres (DSMs) have been evaluated most extensively. Phase II clinical trials have demonstrated their efficacy when co-administered with chemotherapeutic drugs (chemo-occlusion), as measured by tumour response. The therapeutic benefits associated with chemo-occlusion would suggest that this technique might have a potential application as an adjuvant therapy, eg in reducing tumour recurrence after surgical resection in hepatocellular carcinoma, or down-staging a tumour prior to surgical resection. Furthermore, comprehensive management of patients with liver metastases and potential extrahepatic involvement may well be achieved by a combination of DSM chemo-occlusion and systemic chemotherapy. Large, randomised trials are required to access the clinical benefits associated with chemo-occlusion, such as quality of life, time to tumour progression and survival. Other application areas could be the treatment of breast and pancreatic carcinomas.

DSMs are produced by crosslinking a hydrolysed starch with epichlorohydrin in a common emulsion polymerisation process. The DSMs that have been successfully used for chemo-occlusion have a diameter of 45 plus/minus 7 mu m. They are readily degraded in the blood by alpha-amylase, but maintain their integrity for a certain time before they are degraded and disappear from the blood flow. The size of the DSMs has a direct relationship to the place of occlusion along the vascular tree of the target organ. DSMs descend to the arterial capillary level where they are lodged. As the DSMs are deformable, they have the ability to adapt to their vascular surroundings, so providing a more complete blockade of the capillaries.

Approximately 80% of the bloodstream can be temporarily occluded by DSMs for a period of 15-80 min. A cytostatic drug co-administered with the DSMs will consequently be selectively trapped along with the DSMs, enhancing concentrations of the drug in the vicinity of the tumour.

REFERENCES

A complete list of references is available from R. Beck at Cerestar Application Centre Pharma & Chemical.

This article is by J. P. Remon, J. Voorspoels, M. Radeloff, A. N. Patel and R. Beck of Cerestar. For further information contact Roland Beck at Cerestar Application Centre Pharma & Chemical, Havenstraat 84, B-1800 Vilvoorde, Belgium. Tel: Int+32-2-2570611. Fax: Int+32-2-2542659.